Remarks

Claims 52-75 are pending in the subject application. By this Amendment, Applicants have canceled claim 75 and amended claims 53, 55, 56, 63, 64, 67, 68, and 73. Support for the amendments and new claims can be found throughout the subject specification and in the claims as originally filed in the PCT application (see, for example, original claims 1-30 and pages 4-9 of the as-filed application). Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 52-74 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

At the outset, Applicants respectfully request that the amendment filed May 22, 2009 not be entered in this matter and that this submission be entered as the required submission under 37 C.F.R. § 1.114.

Applicants gratefully acknowledge the Examiner's withdrawal of the objections to Figure 1 and the specification and the rejections under 35 U.S.C. § 112, first and second paragraph, and 35 U.S.C. § 103(a).

Claims 55, 63 and 64 are rejected under 35 U.S.C. 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Office Action indicates that there is insufficient antecedent basis for the limitation "the DNA" in claim 56. By this Amendment, claim 56 has been amended to depend from claim 54 and antecedent basis for this language can be found in subpart (c) of claim 54.

The Office Action indicates that there is insufficient antecedent basis for the limitation "the vector" in claim 55. By this Amendment, claim 55 has been amended to depend from claim 53 thereby correcting this inadvertent typographical error.

Claims 63 and 64 are rejected for reciting the limitation "the vector according to Claim 55". Based on the amendment made to claim 55 as indicated above, this rejection is believed to be moot as antecedent basis for this language can be found in claims 53-54.

Claim 63 recites "the DNA sequence coding for a polypeptide of interest". Claim 63 has been amended to correct the dependency of the claim and it is believed that this amendment attends to the antecedent basis issue noted in the Office Action.

The Office Action states that claims 63 and 64 recite "insulator(s)"; however, it is not sufficiently clear whether these claims are referring to the insulator of claim 52 (identified as claim 1 in the Office Action), or some other generically-defined insulator. Hence, the metes and bounds are not clear. Applicants respectfully submit that this language was clear as previously presented and that the insulators referred to in the claims would have been understood to be the insulator(s) consisting of SEQ ID NO: 1. However, by way of the amendments presented herein, it is believed that this issue is now moot.

Claims 63-64 are rejected for depending from a rejected parent claim. Applicants believe that this issue is moot in view of the amendments presented herein.

The Office Action indicates that claim 65 recites the limitation "the DNA"; however, Applicants respectfully assert that the limitation is not contained in the claim. To the extent that the Office Action intended to reject claim 56 on this basis, Applicants note that the dependency of claim 56 has been amended that antecedent basis for the language can be found in claim 54.

Claims 67 and 68 recite "the first subunit" and "the second subunit" and the claims have been rejected on the basis that antecedent basis for this language is lacking in claim 66. Additionally, claims 65-68 are rejected for depending from at least one rejected parent claim. Claims 67-68 have been amended in a fashion that remedies this issue. Accordingly, it is believed that these issues are now moot.

Claim 75 recites that the transfection is stable. However, the scope of such is not clear. The cancellation of this claim remedies this issue. In view of the forgoing amendments to the claims, reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 56 and 65-68 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office Action argues that the support for the previously presented claims is not found in the as-filed specification. Applicants respectfully assert that there is adequate written description in the subject specification to convey to the ordinarily skilled artisan that they had possession of the claimed invention.

In considering whether there is 35 U.S.C. § 112, first paragraph, support for the claim limitation, the examiner must consider not only the original disclosure contained in the summary and detailed description of the invention portions of the specification, but also the original claims, abstract, and drawings. See *In re Mott*, 539 F.2d 1291, 1299, 190 USPQ 536, 542–43 (CCPA 1976) (claims); *In re Anderson*, 471 F.2d 1237, 1240, 176 USPQ 331, 333 (CCPA 1973) (claims); *Hill-Rom Co. v. Kinetic Concepts, Inc.*, 209 F.3d 1337, 54 USPQ2d 1437 (Fed. Cir. 2000) (unpublished) (abstract); *In re Armbruster*, 512 F.2d 676, 678–79, 185 USPQ 152, 153–54 (CCPA 1975) (abstract); *Anderson*, 471 F.2d at 1240, 176 USPQ at 333 (abstract); *Vas-Cath Inc. v. Mahurkar*, 935 F.2d at 1564, 19 USPQ2d at 1117 (drawings); *In re Wolfensperger*, 302 F.2d 950, 955–57, 133 USPQ 537, 541– 43 (CCPA 1962) (drawings). Indeed, it is well accepted that a satisfactory description of a claimed invention may be in the claims or any other portion of the originally filed specification. *See In re Koller*, 613 F.2d 819, 204 USPQ 702 (CCPA 1980) (original claims constitute their own description); accord *In re Gardner*, 475 F.2d 1389, 177 USPQ 396 (CCPA 1973); *accord In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). In this regard, Applicants note that the claims presented by way of preliminary amendment and in subsequent amendments found support, for example, in original claims 2-19 of the PCT application/publication from which this national stage filing originated. Additionally, the as-filed description of the PCT application also provides support for the claims, as now and previously presented (see, for example, page 4, lines 26-29 and pages 5-8). Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested as support for the current and previously presented claims was present in the as-filed PCT application.

Claims 73-75 are rejected under 35 U.S.C. § 112, first paragraph, as nonenabled by the subject specification. The Office Action indicates that the specification is enabled for methods in which the vector contains a promoter operatively linked to a coding sequence of interest, but is not enabled for any embodiment lacking a promoter and operatively-linked coding sequence. Applicants respectfully assert that the claims as filed are enabled; however, the claims have been amended in accordance with the suggestion of the Examiner (support for the amended claim can be found, for Example, in Figure 2 and the descriptions thereof at pages 3 and 11; page 7, lines 27-36; and original

claims 2-24). Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 52-55, 57, 58, 62-64, 70, 71, 73 and 75 are rejected under 35 U.S.C. § 103(a) as obvious over Taun *et al.* (U.S. Patent No. 6,395,549), Recillas-Targa *et al.* (2002), Chung *et al.* (1997) and Henderson *et al.* (U.S. Patent No. 6,432,700). The Office Action states Taun *et al.* teach integrating vectors comprising enhancers, insulators, and promoters to drive the expression of any gene of interest in animal cells. Further, it is taught to use barrier-function sequences to isolate the integrated vector from position effects in the chromatin to avoid silencing. Hence, Taun *et al.* teach that it is known in the art to place barrier-function sequences on both sides of an integrating vector in order to protect it from silencing, and this can be used for the expression of desired transgenes. Further Taun *et al.* teach the use of GFP coding sequences as a reporter for expression, and further to link the expression of such GFP to hCMV to obtain expression in cells, as it is well known that such promoters are widely active in many cell types (absent reason to believe otherwise, this is hCMV-IE1, as such is the standard utilized in the art for constitutive expression). The Office Action states that Recillas-Targa *et al.* teach that the position protection effect of the chicken beta-globin insulator is located in a larger region encompassed by Applicants' SEQ ID NO: 1, and is severable from the enhancer blocking activity. Further, it is stated that Recillas-Targa *et al.* teach that it is normal to utilize two copies of the position-effect on both sides of the vector provide for good isolation from position effects. Lastly, Recillas-Targa *et al.* teach minimization of domain sizes. The Office Action states Chung *et al.* teach that the same insulator as Recillas-Targa *et al.* is active in mammalian cells. The Office Action notes that Henderson *et al.* teach that it is optimal to minimize the size of the other components of the vector, in order to make more room for transgenes which are to be expressed. The Office Action further argues:

> Hence, from this, the Artisan would be motivated to make an integrating vector, comprising two copies of SEQ ID NO 1 on each end of the integrating vector, with the normally present base that Applicant has removed from the sequence, and further to comprise the CMV promoter driving expression of GFP. The Artisan would be so-motivated to provide the minimal sequence of the beta-globin barrier sequence of Recillas-Targa, and do so to express proteins in mammalian cells, as is taught in Chung. In addition, there is a reasonable expectation of success, as the use

> of such barriers was known, the methods of minimization were known, and the methods of utilizing such to express proteins from integrated vectors was known.
>
> However, such, in itself, does not make obvious the further deletion of the base which Applicant's SEQ ID NO: 1 is missing, from that of the known sequence of the chicken beta globin insulator/barrier sequence.
>
> On the other hand, it is clear that the Artisan knew that the important sequences for the barrier functions were those regions that did not bind proteins (e.g., Recillas-Targa, DISCUSSION), and that intervening sequences were not known to be important. Moreover, Applicant's deleted base is within the intervening sequences (e.g., Chung, FIGURE 3, line 5 of the sequence, the penultimate "C" in such line, determined by comparison to Applicant's specification, FIGURE 1).
>
> Hence, it would be obvious to further delete the "C" between the binding regions. The Artisan would have done so to further minimize the size the barrier region. Further the Artisan would have expected success, as such region was not bound by any proteins which cause the barrier effect.
>
> Therefore, the Artisan would make these integrating vectors and transform mammalian cells with such vectors to express transgenes, including GFP for identification of those cells expressing the transgene. The Artisan would have expected success, as the methods were known in the Art.

In this case, the Office Action admits that the combination of references do "make obvious the further deletion of the base which Applicants' SEQ ID NO: 1 is missing, from that of the known sequence of the chicken beta globin insulator/barrier sequence" (see Final Rejection, page 9, paragraph 1). The Office Action then argues that it would have been obvious to delete this single nucleotide on the basis that those skilled in the art knew that the sequences important for barrier functions were those sequences that did not bind proteins, that the deleted base was in a region that did not bind proteins and that it would have been obvious to delete a single nucleotide in order to further minimize the size of the barrier region (a rationale purportedly supported by the teachings of Henderson *et al.* and/or Recillas-Targa *et al.*). Applicants respectfully assert that the claimed invention is not obvious over the cited references.

As noted by the Court of Appeals for the Federal Circuit in *Takeda Chemical Industries, Ltd. V. Alphapharm Pty., Ltd.*, 492 F.3d 1350, (Fed. Cir. 2007):

> Our case law concerning *prima facie* obviousness of structurally similar compounds is well-established. We have held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of

obviousness." *Dillon,* 919 F.2d at 692. In addition to structural similarity between the compounds, a *prima facie* case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure. *In re Grabiak*, 769 F.2d 729, 731-32 (Fed.Cir.1985).

We elaborated on this requirement in the case of *In re Deuel,* 51 F.3d 1552, 1558 (Fed.Cir.1995), where we stated that "[n]ormally a *prima facie* case of obviousness is based upon structural similarity, *i.e.,* an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.* We clarified, however, that in order to find a *prima facie* case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required. *Id.* (citing *In re Jones,* 958 F.2d 347 (Fed.Cir.1992); *Dillon,* 919 F.2d 688; *Grabiak,* 769 F.2d 729; *In re Lalu,* 747 F.2d 703 (Fed.Cir.1984)).

That test for *prima facie* obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.[FN2] While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR,* 127 S.Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.* Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound.

In this case, it is respectfully submitted that a *prima facie* case of obviousness has not been established with respect to the claimed insulator element, a nucleic acid sequence "consisting of SEQ ID NO: 1", vectors containing one or more copies of the insulator consisting of SEQ ID NO: 1, host cells containing such vectors or methods of producing polypeptides comprising the culturing of such host cells under conditions that allow for the production of said polypeptide. As noted above, in order to establish a *prima facie* case of obviousness, it is necessary that the "prior art would have

suggested making the specific molecular modifications necessary to achieve the claimed invention". In this case, there is no teaching or suggestion to delete the cytosine from the known sequence of the chicken beta globin insulator/barrier sequence, and none of the cited references provide any suggestion for making such a modification. Indeed, Recillas-Targa *et al.* already teach the minimal insulator element for the chicken beta globin insulator/barrier sequence (see page 6888, last paragraph), a nucleic acid sequence that includes footprint regions III-V (see page 6886, column 1, paragraph 3 and Figures 4-5). Thus, there would have been no motivation to further reduce the length of this sequence for use within plasmids. To the extent that Henderson *et al.* discuss minimizing elements within expression vectors, Applicants note that those teachings pertain to minimizing the size of heterologous transcriptional regulatory elements (TREs (*e.g.*, promoters and/or enhancer elements; see column 8, around lines 50-60)). This, too, provides no suggestion to make the specific molecular modifications necessary to achieve the claimed invention. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 52-59, 62-67, 69, and 73-75 are rejected under 35 U.S.C. § 103(a) as obvious over Taun *et al.* (U.S. Patent No. 6,395,549), Recillas-Targa *et al.* (2002), Chung *et al.* (1997) and Henderson *et al.* (U.S. Patent No. 6,432,700) and further in view of Perlman *et al.*(2003) and Aldrich *et al.* (1998). The Office Action indicates that Perlman *et al.* teach that CHO cells can be used to express FSH from vectors comprising the alpha and beta subunits. The Office Action states that Aldrich *et al.* teach the use of bicistronic vectors for expression, which provide for reducing the time required to develop cell pools for protein expression. Additionally, claims 52-55, 57, 58, 61-64, 69, 70, 71, 73 and 75 are rejected under 35 U.S.C. § 103(a) as obvious over Taun *et al.* (U.S. Patent No. 6,395,549), Recillas-Targa *et al.* (2002), Chung *et al.* (1997) and Henderson *et al.* (U.S. Patent No. 6,432,700) and in further view of Laus *et al.* (U.S. Patent No. 6,194,152). The Office Action cites Laus *et al.* as teaching expression of thymidine kinase transgenes as a selectable marker in mammalian cells.

As noted above, the combination of Taun *et al.* (U.S. Patent No. 6,395,549), Recillas-Targa *et al.* (2002), Chung *et al.* (1997) and Henderson *et al.* (U.S. Patent No. 6,432,700) fail to provide any suggestion for making the specific molecular modifications necessary to achieve the claimed invention. Laus *et al.*, Perlman *et al.* and Aldrich *et al.* do not remedy this defect in the combined

teaching of Taun *et al.* (U.S. Patent No. 6,395,549), Recillas-Targa *et al.* (2002), Chung *et al.* (1997) and Henderson *et al.* (U.S. Patent No. 6,432,700). Accordingly, it is respectfully submitted that the claimed invention is not obvious over the cited references and reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 52-55, 56, 57, 58, 62-66, 68-74 and 75 are rejected under 35 U.S.C. § 103(a) as obvious over Taun *et al.* (U.S. Patent No. 6,395,549), Recillas-Targa *et al.* (2002), Chung *et al.* (1997) and Henderson *et al.* (U.S. Patent No. 6,432,700) and in further view of Anderson *et al.* (U.S. Patent No. 6,113,898) and Aldrich *et al.* (1998). The Office Action states Anderson *et al.* teach CHO cells being transformed to express the heavy and light chains of antibodies to the human B7.1 and/or B7.2 antigens. The Office Action asserts that Aldrich *et al.* teach the use of bicistronic vectors for expression, which provide for reducing the time required to develop cell pools for protein expression. Likewise, claims 52-55, 56, 57, 58, 62-66, 68-74, and 75 are rejected under 35 U.S.C. § 103(a) as obvious over Taun *et al.* (U.S. Patent No. 6,395,549), Recillas-Targa *et al.* (2002), Chung *et al.* (1997), Henderson *et al.* (U.S. Patent No. 6,432,700), Anderson *et al.* (U.S. Patent No. 6,113,898) and Aldrich *et al.* (1998) and in further view of Adair *et al.* (U.S. Patent No. 6,632,927). As noted above, Taun *et al.* (U.S. Patent No. 6,395,549), Recillas-Targa *et al.* (2002), Chung *et al.* (1997) and Henderson *et al.* (U.S. Patent No. 6,432,700) fail to teach or suggest the specific molecular modifications necessary to achieve the claimed invention. Adair *et al.*, Aldrich *et al.* and Anderson *et al.* fail to remedy this defect in the combination of Taun *et al.* (U.S. Patent No. 6,395,549), Recillas-Targa *et al.* (2002), Chung *et al.* (1997) and Henderson *et al.* (U.S. Patent No. 6,432,700). Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested as a *prima facie* case of obviousness has not been established by the cited combination of references.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including

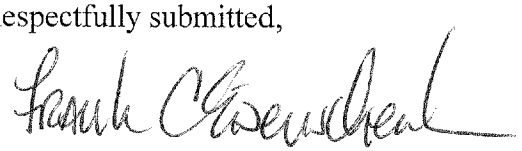
any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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